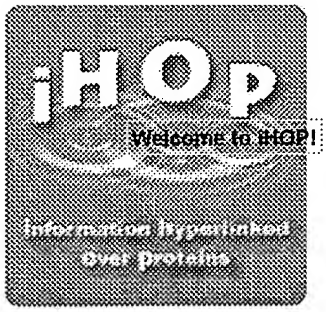
Merriam-Webster Online Dictionary

reside

One entry found for **reside**.

Main Entry: **re·side**
Pronunciation: `ri-'zId`
Function: *intransitive verb*
Inflected Form(s): **re·sid·ed**; **re·sid·ing**
Etymology: Middle English, from Middle French or Latin; Middle French *resider,* from Latin *residEre* to sit back, remain, abide, from *re-* + *sedEre* to sit -- more at SIT
1 a : to be in residence as the incumbent of a benefice or office **b :** to dwell permanently or continuously **:** occupy a place as one's legal domicile
2 a : to be present as an element or quality **b :** to be vested as a right
- re·sid·er *noun*

Pronunciation Symbols



Symbol	Name	Synonyms	Organism
RALBP1	ralA binding protein 1	76-kDa Ral-interacting protein, Dinitrophenyl S-glutathione ATPase, DNP-SG ATPase, RalA binding protein 1, RalBP1, Ral interacting protein 1, RIP, RIP1, RLIP1, RLIP76	Homo sapiens

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UniProt	Q15311, Q59E87
OMIM	605801
NCBI Gene	10928
NCBI RefSeq	NP_006779
NCBI RefSeq	NM_006788
NCBI UniGene	10928
NCBI Accession	BQ224100, BX352266

Homologues of RALBP1 ... new

Definitions for RALBP1 ...

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Transport of **glutathione** conjugates and chemotherapeutic drugs by **RLIP76** ★ (**RALBP1 [?]** ★★): a novel link between **G-protein** and **tyrosine kinase** signaling and drug resistance.

Our studies have shown that **RLIP76** ★ (**RALBP1 [?]** ★★), a 76 kDa Ral-binding, Rho/Rac-GAP and Ral effector protein, is a novel multispecific transporter of **xenobiotics** as well as GS-Es.

RLIP76 ★★ (ral-binding protein, **RalBP1 [?]** ★★) is a non-ABC multi-specific transporter of amphiphilic chemotherapeutic drugs such as doxorubicin (DOX) and glutathione-electrophile conjugates.

This **GAP** region is not required for **RLIP1** ★★★ binding to Ra1.

Transport functions and physiological significance of 76 kDa Ral-binding **GTPase activating protein** (**RLIP76**).

Functional reconstitution of Ral-binding **GTPase activating protein**, **RLIP76**, in proteoliposomes catalyzing ATP-dependent transport of glutathione conjugate of 4-hydroxynonenal.

We have recently shown that **RLIP76** ★★, a ral-binding **GTPase activating protein**, mediates ATP-dependent transport of glutathione-conjugates (GS-E) and doxorubicin (DOX) (S. Awasthi et al., Biochemistry 39,9327,2000).

Concept & Implementation

by Robert Hoffmann

We have recently shown that **RLIP76**, a Ral-binding, **GTPase-activating protein**, is an ATP-dependent transporter of doxorubicin (DOX) as well as glutathione conjugates [Awasthi, S., et al. (2000) Biochemistry 39, 9327-9334].

We have recently demonstrated that a previously known Ral-binding **GTPase activating protein**, **RLIP76**, can also catalyze ATP-dependent transport of various structurally unrelated xeno- and endobiotics irrespective of their net charge (Awasthi et al., 2000, Biochemistry, 39: 9327).

Our recent studies demonstrate that **RLIP76**, a previously known **GTPase-activating protein** catalyzes ATP-dependent, uphill transport of anionic glutathione conjugates as well as of weakly cationic anthracyclines including doxorubicin (Adriamycin), a widely used drug in cancer chemotherapy.

Dinitrophenyl S-glutathione ATPase [?] purified from human **muscle** **catalyzes** **ATP [?]** hydrolysis in the presence of **leukotrienes**.

We now demonstrate that **DNP-SG ATPase [?]** purified from human lung and erythrocyte membranes **catalyzed** the hydrolysis of **ATP [?]** in the presence of **doxorubicin** and its metabolites.

Although stimulation of **ATP [?]** hydrolysis **catalyzed** by **DNP-SG ATPase [?]** has been demonstrated in the presence of several structurally unrelated amphiphilic ions, structural and functional properties of this protein have not been well-defined.

Functional reassembly of ATP-dependent xenobiotic transport by the N- and C-terminal domains of **RLIP76** and identification of **ATP** binding sequences.

Antibodies against **DNP-SG ATPase [?]** immunoprecipitated the **ATP [?]** hydrolyzing activity stimulated by **doxorubicin**, its metabolites, and glutathione conjugates.

Doxorubicin-stimulated **ATP [?]** hydrolysis by **DNP-SG ATPase [?]** was saturable with respect to **doxorubicin** (Km 1.2 and 2.8 microM for the lung and erythrocyte enzymes, respectively).

Mu2, the medium chain of the **AP2** **complex** is shown to **interact** with **RLIP76**.

The best characterized **RalA** signaling pathways involve **RalBP1** and phospholipase D.

The whole cDNA was cloned, and it encodes a 76-kDa polypeptide, **RLIP76**, which also binds **RalA**.

RLIP76, an effector of the **GTPase** Ral, interacts with the **AP2** complex: involvement of the Ral pathway in receptor endocytosis.

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We show also that in vivo endogenous **AP2** and **RLIP76** form a complex and that this in vivo interaction is independent of cells being stimulated by a growth factor.

RLIP76 **ATPase** purified from NSCLC cell lines was about 2-fold more active than that from **SCLC** in the absence of the stimulator dinitrophenyl S-glutathione (206+/-47, n=7 vs. 94+/-22, n=6, nmol/min/mg protein, respectively), or in its presence (340+/-60, n=7 vs. 186+/-32, n=6, nmol/min/mg; p<0.01).

We propose that these pathways are linked through a cascade composed of Ras –> Ra1GDS –> Ra1 –> **RLIP76** –> CDC42/Rac1/Rho, allowing modulation of the **Rho** pathway by the Ras pathway.

Stress-pre-conditioned cells with induced hGST5.8 and **RLIP76** acquired resistance to 4-HNE and H2O2-**mediated** apoptosis by **suppressing** a sustained activation of c-Jun N-terminal kinase and **caspase 3**.

RIP4 (DIK/PKK), a novel member of the **RIP** kinase family, activates NF-kappa B and is processed during apoptosis.

The cells irradiated with UVA for 5 min and allowed to recover for 2 h in normal medium (UVA-preconditioned cells) showed a remarkable induction of hGST5.8, which catalyzes conjugation of 4-HNE to **glutathione** (GSH), and **RLIP76** (Ral **BP-1**), which mediates the transport of the conjugate, GS-HNE.

Ral and **POB1** simultaneously **interacted** with **RalBP1 [?]** in **COS cells**.

These results suggest that **RalBP1 [?]** makes a **complex** with **POB1** and that this complex may provide a link between tyrosine kinase, Src homology 3 (SH3)-containing protein, and Ral.

The binding domain of **RalBP1 [?]** to **POB1** was distinct from its binding domain to Ral.

REPS2/POB1 is an EH domain-containing protein, reported to be involved in signalling via **RalBP1 [?]** and to play a role in endocytosis of **EGF** receptors.

On the other hand, EGF-induced lamellipodial protrusion was inhibited by microinjection of the RalA-binding domains of **RalBP1 [?]** and **Sec5**.

Presence of two transport components in female mouse cLPM, but only one system in the cLPM fraction of male mouse, was confirmed by measuring DNP-SG mediated stimulation of **ATP [?]** hydrolysis (**DNP-SG ATPase [?]** activity).

The structures of two glycosylated compounds (**RIP-1 [?]** and **RIP-2**) isolated from the culture broth of the bacterium were determined to be 3-formyl-23-(O-[beta-D-glucopyranosyl])rifamycin SV and 23-(O-[beta-D-glucopyranosyl])rifampin, respectively.

Importantly, Vpr and **Rip-1 [?]** **coimmunoprecipitated** with the human **GR** as part of an activated receptor complex.

Therefore, in contrast to other TLRs, which use interleukin 1 receptor-associated kinase (**IRAK [?]**) **proteins** to activate **NF-kappa B**, TLR 3-induced **NF-kappa B** activation is dependent on **RIP** kinases.

Ral-binding protein 1 (**RalBP1 [?]**) is a putative effector protein of Ral and exhibits a GTPase **activating** activity for Rac and **CDC42 [?]**.

Upon heat shock, the **Ral [?]** signaling pathway is activated, and the resulting RalGTP binds **RalBP1 [?]**.

The other three genes were annexin XI, human HIV Rev-interacting protein **Rip-1 [?]**, and the human homologue of the ATP-binding **arsA [?]** component of the bacterial arsenite transporter, all of which are known to be widely expressed in human tissues.

Three cDNA isolates, **HAX-1**, eEF-1gamma and **hRIP [?]**, code for **proteins** of a size consistent with in vitro cross- linking studies.

Although **hRIP [?]** is thought to be a general mRNA binding protein, this represents an unreported activity for eEF-1gamma and **HAX-1**.

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This tissue-specific determinant(s) was detected in the **RIP-1 [?]** and **RIP-2 [?]** human pancreatic adenocarcinomas carried as xenografts in

athymic nude mice.

However, pretreatment of the cells with the **Hsp90 [?]** inhibitor geldanamycin, which leads to proteasome-mediated degradation of receptor interacting protein 1 (**RIP1 [?]**), reverts FKBP-FADD-induced **necrosis** to apoptosis.

One such transporter is **DNP-SG ATPase**, whose identity has recently been established with **RLIP76**, a Ral binding **GTPase activating protein** known to be involved in the Ras-Rho-Ral mediated signaling mechanism.

We have recently demonstrated that **RLIP76**, a Ral-binding **GTPase activating protein** mediates ATP-dependent transport of **glutathione** (GSH) conjugates of electrophiles (GS-E) as well as **doxorubicin** (DOX), and that it is identical with **DNP-SG ATPase**, a GS-E transporter previously characterized by us in **erythrocyte** membranes (Awasthi et al. Biochemistry 39, 9327-9334).

Earlier studies from our laboratories have shown that **RLIP76**, a previously described Ral-binding **GTPase activating protein** (Jullien-Flores et al., 1995, J. Biol. Chem. 270: 22473), is identical with the xenobiotic transporter **DNP-SG ATPase**, and can catalyze ATP-dependent transport of glutathione-conjugates as well as doxorubin (Awasthi et al., 2000, Biochemistry, 39: 9327).

Present studies have identified the **ATP binding** sites in **RLIP76**, and show that DOX and COL transport can be reconstituted by two fragments of **RLIP76**.

The photoaffinity labeling of **DNP-SG ATPase [?]** (38 kDa) was saturable with respect to 8-azido **ATP [?]** (Kd = 2 microM), indicating that the enzyme was capable of specific and saturable binding to **ATP [?]**.

This fragment was absent from all **SCLC**, suggesting the possibility that the activity of **RLIP76** in **SCLC** and NSCLC is differentially regulated through post-translational modifications.

Consistent with the greater **RLIP76** ATPase activity in NSCLC, DOX transport in artificial proteoliposomes reconstituted with purified **RLIP76** from NSCLC was 1.8-fold greater than in **SCLC**.

Anti-RLIP76 IgG, which recognized only **RLIP76** in crude extracts of both **SCLC** and NSCLC, inhibited 67+/-4% (n=12 cell lines) of total DOX transport in crude membrane vesicles from both **SCLC** and NSCLC.

POB1 **interacted** with **RalBP1 [?]** in **COS cells** and the C-terminal region of **POB1** was responsible for this interaction.

The binding of **POB1** to **RalBP1 [?]** did not affect the GTPase activating activity of **RalBP1 [?]**.

The **RalBP1 [?]** associated Eps-homology domain protein, **Reps1**, is tyrosine-phosphorylated in response to **EGF** stimulation of cells.

To clarify the function of **RalBP1 [?]**, we isolated a novel protein that interacts with **RalBP1 [?]** by yeast two-hybrid screening and designated it **POB1** (partner of RalBP1).

The intracellular concentrations of 4-HNE are regulated through a coordinated action of GSTs (**GSTA4-4** and hGST5.8) which conjugate 4-HNE to GSH to form the conjugate (GS-HNE) and the transporter 76 kDa Ral-binding **GTPase activating protein** (**RLIP76**), which catalyze ATP-dependent transport of GS-HNE.

POB1 is a **binding protein** of **RalBP1 [?]** and has the

Eps15 homology (EH) domain.

RalBP1 [?], **POB1**, Epsin, and **Eps15** were all phosphorylated in mitotic phase.

Internalization of **EGF** and **insulin** was not affected by full-length **RalBP1 [?]** which is an effector protein of Ral, but was inhibited by its C-terminal region which binds directly to Ral and **POB1**.

However, internalization of **transferrin [?]** was unaffected by Ral, **RalBP1 [?]**, **POB1** and their mutants.

Furthermore, **RLIP76** differentiates **AP2** from **AP1** in vivo as RLIP76 differentiates mu2 from mu1 in vitro and in two hybrid assays.

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In a second step, **TRADD** and **RIP1** **associate** with **FADD** and caspase-8, forming a cytoplasmic complex (complex II).

Using immunological approaches, the present studies were designed to elucidate the relative contributions of **RLIP76**, **MRP1**, and **P-glycoprotein** (**Pgp**), in the ATP-dependent transport of GS-E and DOX in human **erythrocytes**.

In the GTP-bound state, Ral proteins bind to **RalBP1 [?]**, a **GTPase-activating protein** for **CDC42 [?]** and Rac GTPases.

RIP1 [?] and its homologs, **RIP2** and **RIP3**, form part of a family of Ser/Thr kinases that regulate signal transduction processes leading to NF-kappa B activation.

POB1 [?] and **RalBP1 [?]** **function** downstream of small G protein **Ral** and regulate receptor-mediated endocytosis.

Trif [?] recruited the kinases receptor interacting protein (RIP)-1 and **RIP3 [?]** through its **RIP** homotypic interaction motif.

Taken together with the observation that **EGF** and **insulin** activate Ral, these results suggest that Ral, **RalBP1 [?]** and **POB1** transmit the signal from the receptors to Epsin and **Eps15**, thereby regulating ligand-dependent receptor-mediated endocytosis.

RalBP1 [?] and **POB1**, the downstream molecules of **small GTP-binding protein Ral [?]**, are involved in receptor-mediated endocytosis together with Epsin and **Eps15**.

When tested, **RIP1** could **activate** the GTPase activity of **CDC42** and, to a lesser extent, **Rac1** but not **RhoA**, Ras, or Ral.

RalBP1 [?], **POB1**, Epsin, and **Eps15** formed a **complex** with alpha-adaptin of **AP-2 [?]** in Chinese hamster ovary cells, but the formation was reduced in mitotic phase.

The initial **plasma membrane** bound complex (complex I) consists of **TNFR1**, the adaptor **TRADD**, the kinase **RIP1**, and **TRAF2** and rapidly signals activation of **NF-kappa B**.

Concurrently, **HSF1 [?]** is activated, leaves the **RalBP1 [?]** x **HSF1 [?]** x **HSP90 [?]** x alpha-tubulin heterocomplexes, and translocates into the nucleus, where it then activates transcription.

Bridging **Ral** GTPase to **Rho** pathways. **RLIP76**, a **Ral** effector with CDC42/Rac **GTPase-activating protein** activity.

This protein also bears a region of homology with GTPase-activating protein (GAP) domains that are involved in the regulation of GTPases of the Rho family and, indeed, **RLIP1** displays a **GAP** activity

acting upon **Rac1** and **CDC42**, but not **RhoA**.

Furthermore, transient cotransfection of **HSF1 [?]** and the constitutively active form of **RalA** (RalA23V), an upstream activator of the **RalBP1 [?]** signaling pathway, increases the heat-inducible expression of **HSP70 [?]**, whereas the dominant negative form (RalA28N) suppresses **HSP70 [?]** expression.

Purified recombinant **RLIP76**: (1) had **ATPase** activity stimulated by DNP-SG or **doxorubicin** (DOX), and the K(m) values of **RLIP76** for **ATP [?]**, DOX, and DNP-SG were similar to those reported for **DNP-SG ATPase [?]**; (2) upon reconstitution with asolectin as well as with defined lipids, catalyzed ATP-dependent transport of DNP-SG and DOX with kinetic parameters similar to those of **DNP-SG ATPase [?]**; (3) when transfected into **K562 cells**, resulted in increased resistance to DOX, and increased ATP-dependent transport of DNP-SG and DOX by inside-out membrane vesicles from transfected cells; (4) direct uptake of purified **RLIP76** protein into mammalian cells from donor proteoliposomes confers DOX resistance.

We show that **RalBP1 [?]** and **HSF1 [?]** interact in vivo, and transient cotransfection of **HSF1 [?]** and **RalBP1 [?]** into **hsf1 [?]** (-/-) mouse embryo fibroblasts **represses HSP70** expression.